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To Study the Effect of Ursodeoxycholic Acid in Lowering Neonatal Non – Hemolytic Hyperbilirubinemia: A Randomized Control Study.

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ABSTRACT

Background: Hyperbilirubinemia is a common and in most cases, a benign problem in neonates. Conventional treatment for severe indirect hyperbilirubinemia consists of phototherapy and exchange transfusion. Phototherapy, which is the main treatment modality has its own side effects and it also upsets maternal and fetal interactions. So there is a need for adjuvant therapies to decrease duration of phototherapy and hospital stay. Objective: This study was planned to assess the role of UDCA in decreasing the duration of phototherapy in neonatal hyperbilirubinemia. **Methods:** Study setting: Pediatrics department, Bebe Nanki Mother & Child Care Centre, GMC Amritsar. Participants: 100 newborns with bilirubin levels in phototherapy range. Study design: Double blind, placebo controlled study. Participants were divided into two groups and UDCA (10mg/kg/d) and microcrystalline cellulose were given to group A and group B respectively. Outcome variables: Rate of fall of bilirubin levels in both the groups and total duration of phototherapy needed in both groups. **Results:** Mean duration of phototherapy was 36.26±8.41 hours in group A and 38.94±9.86 hours in group B. P value was 0.147 that is statistically not significant. Level of fall of bilirubin in both groups at 12hrly intervals were also compared and difference was not statistically significant. **Conclusion:** UDCA administration to the neonates receiving phototherapy does not hasten the fall in bilirubin levels and does not reduce the time of phototherapy significantly.

Keywords: Hyperbilirubinemia, Ursodeoxycholic Acid, Jaundice.

INTRODUCTION

Jaundice is observed during the 1st week in approximately 60% of term and 80% of preterm neonates.[1] The yellow colour usually results from the accumulation of unconjugated, nonpolar, lipid soluble bilirubin pigment in the skin.[2] Although in most cases, hyperbilirubinemia in neonates is physiological and benign, bilirubin is a potential neurotoxin. Term and late preterm infants are at risk for bilirubin-induced neurological dysfunction (BIND) when TSB concentrations are ≥25 mg/dL.[3,4] At this threshold, unconjugated bilirubin, which is not bound to albumin (also referred to as "free" or unbound bilirubin), can enter the brain and cause cell death by apoptosis (programmed cell death) and/or necrosis.[]5 This can lead to kernicterus and can manifest as permanent sequlae of disorders of vision, hearing, gait, speech and cognition.

Non pharmacological treatment modalities for hyperbilirubinemia mainly include phototherapy and exchange transfusion. Phototherapy is the main modality used nowadays. It has dramatically reduced the need for exchange transfusion.[6] But it has its own side effects eg. Insensible water loss leading to water and electrolyte imbalance, retinal degenerative changes, tanning (bronze baby syndrome).[7] It also upsets maternal and neonatal interactions. Therefore using adjuvant pharmacological therapies which can reduce the duration of phototherapy, its side effects and hospital stay can be highly effective and useful.

Many pharmacological agents have been tried in past. eg. metalloporphyrins,[8] phenobarbitone,[9] clofibrate,[10] Gemfibrozil etc.[11] but none has

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become the standard of care. Ursodeoxycholic acid (UDCA) (3α,7β dihydroxy-5β-cholanic acid) is a tertiary bile acid which is normally present in human bile, but in a low concentration of only 3% of total bile acids. It protects liver cells against oxidative damage, apoptosis and also stimulates biliary secretion of bile acids.[12,13] This study was planned to assess the role of UDCA in lowering neonatal non hemolytic hyperbilirubinemia.

MATERIALS AND METHODS

This study is a double blind, randomized, placebo controlled study that was performed on newborns with neonatal hyperbilirubinemia admitted to Sick Newborn Care Unit (SNCU) of Bebe Nanki Maternal and Child Health Care Centre of Government Medical College, Amritsar from June 2017 to May 2018.

A total of 100 babies were taken, 50 in each group named A and B. Enrolment was done only after taking informed consent from the parents / guardians of the babies. Ethical clearance for the study was taken from institute's ethical committee.

Inclusion criteria:

Newborns with gestation >34 weeks with non hemolytic jaundice requiring phototherapy according to American Academy of Pediatrics charts.[14]

Exclusion Criteria

Any evidence of hemolytic jaundice, sepsis, infant of diabetic mother, direct bilirubin >2mg/dl, G6PD deficient neonates, TSB in exchange zone, severe birth asphyxia, large external/ internal blood collections, hypothyroidism, necrotising enterocolitis / GIT malformation, contraindication for oral feeding.

By a web based random generator15 method neonates meeting the inclusion criteria were divided into two groups (A and B) by a person not involved in the study. Group A (case group) received oral UDCA 10 mg/kg/day divided 12hourly in addition to phototherapy. Group B (control group) received phototherapy plus placebo. UDCA available in tablet form (150mg) was used for this study. Tablets were divided into small sachets containing 10 mg of drug each. Total serum bilirubin (TSB) levels were measured at the time of enrolment and then every 12 hourly till the bilirubin levels became less than phototherapy range. Comparison of TSB levels and duration of phototherapy levels for both the groups was done by appropriate tests and P value was calculated. Caregivers and those who measured the outcome were blinded to the allocated intervention.

RESULTS

[Table 1] shows that the baseline characters like age, gestational age, sex, birth weight and bilirubin levels at enrolment were comparable in both the groups, with no significant difference statistically. Other characters like birth order, place of delivery, mode of delivery, maternal and baby blood groups, TSH and G6PD levels were also comparable in both the groups.

Table 1: Showing the baseline characters in both the groups.

S. No.	Baseline Characters	Group A	Group B	P value
1.	Age at presentation(days)	3.92±1.65	3.86±1.39	0.845
2.	Gestational age (weeks)	37.70±1.65	37.66±1.47	0.899
3.	Sex (male, female %)	72 , 28	74 , 26	0.974
3.	Birth weight (kg)	2.64±0.49	2.57±0.49	0.481
4.	Bilirubin levels at enrolment (mg/dL)	16.79±1.74	16.87±1.68	0.809

The mean of total bilirubin in group A was 16.79±1.74 and in group B was 16.87±1.68 (p 0.809). The mean fall of total bilirubin in the two study groups at the time of hospitalization and 12, 24, 36, 48, 60, and 72 hours after hospitalization is presented in [Table 2]. The results of stats show that the fall of bilirubin in both the groups was similar and p value was not significant statistically.

Table 2: Decline In Bilirubin Levels After Hospitalisation.

TSB	Group A		Group B		P value
	Mean	SD	Mean	SD	
At admission	16.84	1.75	17.00	1.70	0.632
12 hours	15.41	1.55	15.90	1.51	0.110
24 hours	14.08	1.74	14.73	1.68	0.065
36 hours	13.27	1.71	13.77	1.75	0.235
48 hours	11.43	4.26	13.08	1.95	0.215
60 hours	11.60	0.00	13.73	1.20	0.265

Also maximum number of patients in group A had the peak TSB levels in group 16.1-17 and 17.1-18. This is similar to peak TSB levels recorded in group B i.e. between 15.1-16, 16.1-17 and 17.1-18. P value calculated was 0.743 i.e. the peak levels in both the groups were statistically similar. [Figure 1]

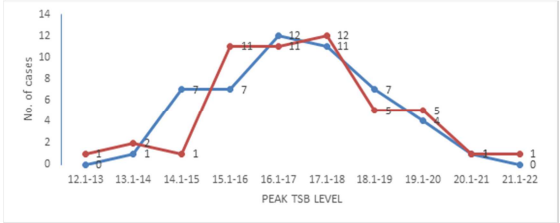

Figure 1: Showing the peak TSB levels in both the groups.

The mean duration of phototherapy needed to the decrease TSB levels below phototherapy range in group A was 36.26±8.41 hours and that in group B was 38.94±9.86 hours. P value was 0.147 that was not significant stastistically [Figure 2].

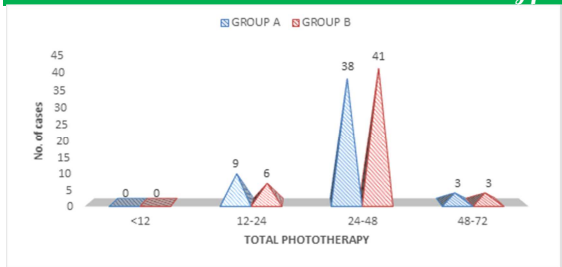

Figure 2: showing the mean duration of phototherapy needed in both the groups.

DISCUSSION

This study was a prospective, double blind, placebo controlled, randomized study. All the cases with any evidence of isoimmune hemolytic disease were excluded. Results showed that study and control groups were comparable in all aspects and there was no statistical significance in general characters of two groups. Mean age of presentation in group A was 3.92±1.65 and in group B was 3.86±1.39 days which is in accordance with the normal age of appearance of physiological jaundice in newborns.[16]

We found that the rate of fall of bilirubin in both the groups after 12, 24, 36, 48 and 60 hours of hospitalisation were similar with no statistical difference. This is in contrast to previous studies by Hassan et al,[17] and Honar et al,[18] who found significant difference in UDCA treated group. A recent study by Jafari et al,[19] in 2017 also reported rapid fall in TSB levels in UDCA treated group, especially in first 8 hours of phototherapy.

The mean duration of total phototherapy needed for group A was 36.26±8.41 hours whereas for group B was 38.94±9.86 hours. P value is 0.147 i.e. the difference is not significant statistically. This is also in contrast to studies by Honar et al,[18] (15.5±6 hours in case group v/s 44.6±13.3hours in control group) and Hassan et al,[17] (23.2±5.6hours v/s 41.1±7.2hours in case and control respectively) that showed a significant decrease in duration of time required for phototherapy. This contradiction between the results of these studies and our study can be explained by the fact that the mechanism of action of UDCA in decreasing unconjugated bilirubin levels is not exactly clear and amount of decrease in enterohepatic circulation of bilirubin due to UDCA has not been proven or quantified so far. Both the above studies proposed that UDCA increases bilirubin turnover by increasing the fecal disposal of unconjugated bilirubin decreasing the amount of enterohepatic circulation and hence decreasing the levels of UCB in blood. However, none of them measured the fecal bilirubin levels in study and control groups so as to prove their statements. Also, Mendez – Sandez et al,[20] in 1990 did a study on rodents and proved that UDCA results in increased enterohepatic circulation and increased the blood levels of unconjugated bilirubin.

No significant side effects of UDCA were reported in the study. This is similar to studies by Hassan et al,[17] and Honar et al,[18] who also did not report any side effect of UDCA in their studies. The safety and efficacy of UDCA has been reported in some previous studies also.[21]

CONCLUSION

From the different observations of our study, we conclude that UDCA when given along with phototherapy to the neonates suffering from non hemolytic hyperbilirubinemia does not have any statistically significant effect on the peak TSB levels, rate of fall of bilirubin and total duration of phototherapy needed for treatment. No short term side effects were noted in UDCA treated patients during the study period. Further studies with larger sample size and/or with change of dosing schedule may be undertaken in future to prove the beneficial effect of UDCA, if any.

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